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EXAMINER
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1644	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/809,753	Applicant(s) GELFAND ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *16-19 and 31-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 20-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-37 are pending.

2. Applicant's election with traverse of Group I, Claims 1-15 and 20-30 drawn to a method to inhibit airway hyperresponsiveness in a mammal comprising administering to a mammal an agent wherein the agent is a CGRP peptide, a fragment or a homologue thereof filed 5/14/02, is acknowledged. The traversal is on the grounds that Group I are drawn to the use of CGRP proteins, fragments and homologues to bind to and activate a CGRP receptor to inhibit airway hyperresponsiveness and Group II are drawn to the same method but the CGRP receptor binding agent is an antibody. This is not found persuasive because of the reasons set forth in the restriction mailed 8/14/01. The inventions of Groups I and II are methods of treatment using distinct products (protein versus antibody), which differ with respect to their structures, physiochemical properties, and one cannot be substituted for the other. Further, the methods of treating using protein and antibody differ respect to their Class and subclass. A prior art search of one would not encompass the other. It is a burden to search more than one invention. Therefore, the requirement of Group I and Groups II-III is still deemed proper and is therefore made FINAL.

3. Claims 16-19 and 31-37 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-15 and 20-30 drawn to a method to inhibit airway hyperresponsiveness in a mammal comprising administering to a mammal an agent wherein the agent is a CGRP peptide, a fragment or a homologue thereof are being acted upon in this Office Action.

5. The drawings, filed 8/9/01, are not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review. Appropriate action is required.

6. Claim 27 is objected because "nedocrimal" should have been "Nedocromil". Correction is required.

7. The disclosure is objected to because of the following informality: (1) "nedocrimal" on page 44 line 24 should have been "Nedocromil".

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-15 and 20-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method to inhibit airway hyperresponsiveness in a mammal comprising administering to a mammal a calcitonin gene related peptide (CGRP) that binds to and activates a calcitonin gene related peptide (CGRP) receptor in the lungs of said mammals, wherein said mammal has or is at risk of developing, airway hyperresponsiveness, **does not** reasonably provide enablement for (1) a method to inhibit airway hyperresponsiveness in a mammal comprising administering to a mammal *any* agent, *any* fragment of CGRP, *any* homolog of CGRP, *any* product of rational drug design that binds and activates CGRP receptor in the lungs of said mammals, wherein said mammal has or is at risk of developing, airway hyperresponsiveness, (2) a method to inhibit airway hyperresponsiveness in a mammal comprising administering to a mammal *any* agent, *any* fragment and *any* homolog of CGRP mentioned above in conjunction with *any* CGRP receptor activity modifying protein (RAMP) that binds and activates CGRP receptor in the lungs of said mammals, wherein said mammal has or is at risk of developing, airway hyperresponsiveness, (3) the said method wherein the airway hyperresponsiveness is allergen-induced airway hyperresponsiveness, (4) the said method wherein said mammal has been sensitized to an allergen and has been exposed to or is at risk of being exposed to, an amount of said allergen that is sufficient to induce airway hyperresponsiveness (AHR) in said mammal in the absence of said agent, (5) the said method further comprises monitoring said mammal to detect whether AHR in said mammal is inhibited, wherein if AHR is detected in said mammal, additional amounts of said agent are administered until AHR is not detected in said mammal, (6) the said method wherein said agent is administered within a time period between 48 hours or less prior to exposure to an AHR provoking stimulus that is sufficient to induce AHR and within 48 hours or less after the detection of the first symptoms of AHR, (7) the said method wherein the agent is administered upon the detection of

the first symptoms of AHR, or within 1 hours, 12 hours, or within 2 hours or less prior to exposure to a AHR provoking stimulus that is sufficient to induce AHR, (8) the said method wherein the agent is administered to said mammals every one to two days, (9) the said method wherein agent is administered at a dose from about 0.1μg per kilogram, and about 20 μg per kilogram body weight of said mammal, or at a dose from about 0.1μg per kilogram, and about 10 μg per kilogram body weight of said mammal, or at a dose from about 0.1μg per kilogram, and about 5 μg per kilogram body weight of said mammal, (10) the said method wherein said agent is targeted to cells in the lung of said mammals selected from the group consisting of smooth muscle cells and epithelial cells, (11) the said method wherein said agent is administered by direct delivery of said agent to the lung by aerosol delivery or by parenteral delivery or by oral delivery, (12) the said method wherein administration of said agent reduces the airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5%, (13) the said method wherein said agent is administered to said mammal in conjunction with another agent such as corticosteroids (oral, inhaled and injected), β-agonist (long or short acting), leukotriene modifiers (inhibitors or receptor antagonists), antihistamines, phosphodiesterase inhibitors, sodium cromoglycate, nedocrimal and theophylline, (14) the said method wherein said agent is administered in a pharmaceutically acceptable excipient, and (15) the said method wherein said mammal is a human for allergen induced airway hyperresponsiveness. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method to inhibit airway hyperresponsiveness (AHR) in mice sensitized to ovalbumin using only αCGRP protein. The inhibition of AHR can be block by a specific CGRP peptide (8-37 residues of the full-length αCGRP protein), which is a CGRP

receptor antagonist. The specification defines the term "CGRP receptor agonist" on page 25 as any compound, any agent, including but not limited to antibody, CGRP homologue, any suitable product of drug design such as mimetic of CGRP. The specification on page 28, line 12-13, defines a CGRP protein includes protein homologues or mimetic of CGRP; the term "homologue" is referred to peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but limited to methylation, glycosylation, phosphorylation...addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification).

The specification does not teach how to make and use *any* agent, *any* fragment of CGRP, *any* homologue of CGRP, *any* product of rational drug design that binds and activates CGRP receptor for a method to inhibit airway hyperresponsiveness in a mammal induced by allergen. There term "agent" does not convey the specific structure such as amino acid sequence, chemical properties and function. Since the agent could be DNA, RNA, protein, peptide, antibody, RNA, and small organic molecule, there is insufficient guidance as how to make any agent mentioned above for a method to inhibit airway hyperresponsiveness induced by allergen in a mammal. Further, there is no guidance as to which amino acid residues within the full-length CGRP could be deleted, substituted, or added such that the resulting peptide would maintain both structure and function as the full length CGRP, in turn, for inhibiting airway hyperresponsiveness. Other than αCGRP, there are no working examples demonstrating that any agent, fragment and homologue of CGRP, and any products of rational drug design mentioned above could be use for a method to inhibit airway hyperresponsiveness.

Zhu *et al* (PTO 1449) teach calcitonin gene-related peptide (CGRP) may play different physiological and pathophysiological roles in airway regulation in different species such as horse, human Sprague-Dawley rat, and mouse (See Discussion, in particular).

Given the indefinite number of undisclosed agent, fragment of CGRP, homologue of CGRP, and product of rational drug design that may play different physiological and pathophysiological roles in airway regulation in different species, it is unpredictable which undisclosed agent would be useful for inhibiting airway hyperresponsiveness.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more

specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

10. Claims 1-15 and 20-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for a method to inhibit airway hyperresponsiveness in a mammal comprising administering to a mammal *any* agent, *any* fragment of CGRP, *any* homolog of CGRP, *any* product of rational drug design that binds and activates CGRP receptor in the lungs of said mammals, wherein said mammal has or is at risk of developing, airway hyperresponsiveness, (2) a method to inhibit airway hyperresponsiveness in a mammal comprising administering to a mammal *any* agent, *any* fragment and *any* homolog of CGRP mentioned above in conjunction with *any* CGRP receptor activity modifying protein (RAMP) that binds and activates CGRP receptor in the lungs of said mammals, wherein said mammal has or is at risk of developing, airway hyperresponsiveness.

The specification discloses only a method to inhibit airway hyperresponsiveness (AHR) in mice using only αCGRP protein and the inhibition of AHR can be block by a CGRP peptide (8-37 residues of the full-length αCGRP protein), which is a CGRP receptor antagonist. The specification defines the term "CGRP receptor agonist" on page 25 as any compound, any agent, including but not limited to antibody, CGRP homologue, any suitable product of drug design such as mimetic of CGRP. The specification on page 28, line 12-13, defines a CGRP protein includes protein homologues or mimetic of CGRP; the term "homologue" is referred to peptide which differs from a naturally occurring peptide by modification such as deletion, amino acid substitution, including but limited to methylation, glycosylation, phosphorylation...addition of glycosylaphosphatidyl inositol (See page 34, lines 9-17 of specification).

With the exception of the specific αCGRP and CGRP peptide antagonist mentioned above for a method of inhibiting airway hyperresponsiveness, there is insufficient written description about the structure associated with function of *any* agent, *any* fragment of CGRP, *any* homolog of CGRP, *any* product of rational drug design that binds and activates CGRP receptor in

conjunction with or without *any* CGRP receptor activity modifying protein (RAMP) for a method of inhibiting airway hyperresponsiveness. Given the lack of a written description of *any* additional representative species of agent, fragment of CGRP, homolog of CGRP, product of rational drug design that binds and activates CGRP receptor for a method of inhibiting airway hyperresponsiveness, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-5, 8-9, 11, 20, 23, 26 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagase *et al* (Am J Respir Crit Care Med 154: 1551-56, 1996; PTO 1449).

Nagase *et al* teach a method of inhibiting airway hyperresponsiveness (AHR) in a mammal such as Guinea pig comprising administering to said Guinea pig an agent such as Calcitonin Gene-related peptide (CGRP) that binds to and activates a calcitonin gene related peptide receptor in the lungs exposed to allergen such as methacholine induced airway hyperresponsiveness (See page 154, column 2, Effects of CGRP (8-37) and CGRP on Methacholine and Endothelin-1 induced constriction, Figs 2-3, in particular). Nagase *et al* further teach a CGRP peptide (8-37) that can block the effect of Calcitonin Gene-related peptide (CGRP) (See page 154, column 2, Effects of CGRP (8-37) and CGRP on Methacholine and Endothelin-1 induced constriction, Figs 2-3, in particular). The reference method further comprises monitoring the animal to detect whether AHR is inhibited (See Methods, in particular). The reference agent is administered two minutes, which is between 48 hours or less, prior to exposure to an AHR provoking stimulus such as hyperpea challenge or methacholine (See page 135, column 1, Effects of CGRP (8-37) and CGRP on hyperpnea induced constriction, in particular). Claims 8-9 are

included in this rejection because the reference teaches administering CGRP two minutes prior to exposure to methacholine, and two minutes is within 12 hours, 2 hours or less prior to exposure to methacholine. Nagase *et al* teach administering Calcitonin Gene-related peptide (CGRP) at a dose about 0.05, 0.1, or .2 mg/kg or CGRP peptide (8-37) at a dose of ranging from 0.1, 0.2, or 0.4 mg/kg body weight of the animal (See page 154, Method in particular). The reference Calcitonin Gene-related peptide (CGRP) and CGRP peptide (8-37) target the cells in the lung such as smooth muscle cell that plays a role in airway constriction and epithelial cells (See Fig 6, in particular). The reference Calcitonin Gene-related peptide (CGRP) and CGRP peptide (8-37) is administered by injection (perenteral) in a pharmaceutically acceptable excipient such as saline (See page 154, column 1, Methods, in particular). Thus, the reference teachings anticipate the claimed invention.

13. Claims 1-11, 21-24, 27, 29 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,858,978 (Jan 1999; PTO 1449) or US Pat No. 5,635,478 (June 1997; PTO 892).

The '978 patent teaches a method of using agent such as calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat for a method of inhibiting acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness, in human (See column 5, lines 12-13, column 7, lines 45-49, claims of '978 patent, in particular). The reference agents are administered into the respiratory tract such as the lung by aerosol spray (See column 7, lines 45-49, in particular) or administered orally such as tablet or sublingual (See column 6, lines 3-7, in particular). The '978 patent teaches the reference method is useful in treatment of a variety of acute and chronic inflammatory respiratory disorders by administering CGRP alone and in combination with other agents such as cortisone, which is a corticosteroid, or phosphodiesterase inhibitor conventionally used to treat such diseases (See column 5, lines 36-39, lines 47-53, in particular). The '978 patent teaches the pharmaceutical composition comprises an effective unit dosage at a concentration effective to evoke the desired response by the route appropriate for the particular pharmaceutical carrier (See column 7, lines 6-61, in particular). The '978 patent teaches that the reference agents are administered in multiple successive dosages, spaced as frequently as 6-12 hours apart or as long as six weeks until symptomatic relief is obtained (See column 7, lines 50-55, in particular) or every 24 hours or longer (See column 7, lines 35, in particular).

The '478 patent teaches a method of using agent such as calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat for a method of inhibiting acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness, in human (See column 13, lines 1-6, column 2, lines 39-66 column 3, lines 1-8, in particular). The reference agents are administered into the respiratory tract such as the lung by aerosol spray (See column 6, lines 35, in particular) or administered orally (See column 7, line 3, in particular) or administered by parenterally (See column 6, lines 37-38, in particular). The '478 patent teaches the reference agents are useful in treatment of a variety of acute and chronic inflammatory respiratory disorders, by administering CGRP alone or in combination with other agents such as cortisone, which is a corticosteroid, or phosphodiesterase inhibitor which conventionally used to treat such diseases (See column 5, lines 36-39, lines 47-53, in particular). The '478 patent teaches the pharmaceutical composition comprises an effective unit dosage at a concentration effective to evoke the desired response by the route appropriate for the particular pharmaceutical carrier (See column 6, lines 60-67 bridging column 7, lines 1-10, in particular). The '478 patent teaches the reference agents is administered in multiple successive dosages, spaced as frequently as 6-12 hours apart or as long as six weeks until symptomatic relief is obtained (See column 7, lines 37-51, in particular). Claims 2-3 are included in this rejection because asthma induced airway hyperresponsiveness is due to inhalation or exposure to allergen. Claim 6 is included in this rejection because the references teach the reference agents are administered to ameliorate the symptoms associated with asthma. Claims 7 and 9 are included in this rejection because the '978 patent teaches administering CGRP to inhibit acute inflammation disorder such as asthma and the recitation of administering within 1 hour after the detection of the first symptoms of AHR or administered within 2 hours or less is within the purview of one skill in the art at the time the invention was made to intervene by administering CGRP as taught by the '978 and the '478 patents. Thus, the reference teachings anticipate the claimed invention.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1 and 25 are rejected under 35 U S.C. 103(a) as being unpatentable over Nagase *et al* (Am J Respir Crit Care Med 154: 1551-56, 1996; PTO 1449) or US Pat No. 5,858,978 (Jan 1999; PTO 1449) or US Pat No. 5,635,478 (June 1997; PTO 1449) each in view of Suissa *et al* (Ann Intern Med 126(3): 177-83, Feb 1997; PTO 892).

The teachings of Nagase *et al*, the '978 patent and '478 patent have been discussed supra.

The claimed invention as recited in claim 25 differs from the reference only that the agent reduces the airway hyperresponsiveness of the mammal such that the FEV1 value of said mammal is improved by at least about 5%.

Suissa *et al* teach leukotriene receptor antagonist such as zafirluast and beta agonist treatment is more effective than beta-agonist alone in treating mild-to-moderate asthma (See abstract, in particular). Suissa *et al* teach patients with mild-to-moderate asthma, which have a decrease in forced expiratory volume in 1 s (FEV1) at least 55% of the predicted value and had demonstrated bronchial hyperresponsiveness, reduces airway hyperresponsiveness, zafirlukast alone improves bronchial hyperresponsiveness by 89%, which is at least 5% improvement (See entire document, abstract, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the leukotriene receptor antagonist or beta agonist as taught by Suissa *et al* with the Calcitonin Gene-related peptide (CGRP) as taught by Nagase *et al* or to substitute the corticosteroid, or the phosphodiesterase as taught by the '978 or the '478 patent for the leukotriene receptor antagonist or the beta agonist as taught by Suissa *et al* for a method to inhibit airway hyperresponsiveness in a mammal comprising administering to said mammal an agent in conjunction with other agents such as β-agonists, leukotriene modifiers (inhibitors or receptor antagonists. From the combined teachings of the references, it is apparent

that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Suissa *et al* teach any leukotriene receptor antagonist and beta agonist treatment is more effective than beta-agonist alone in treating mild-to-moderate asthma (See abstract, in particular) and zafirlukast alone improves bronchial hyperresponsiveness by 89%, which is at least 5% improvement (See entire document, abstract, in particular).

17. Claims 1 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagase *et al* (Am J Respir Crit Care Med 154: 1551-56, 1996; PTO 1449) or US Pat No. 5,858,978 (Jan 1999; PTO 1449) or US Pat No. 5,635,478 (June 1997; PTO 1449) each in view of Drazen *et al* (Am J Respir Crit Care Med 157(2): S233-7, June 1998; PTO 892) or Abraham *et al* (Pulm Pharmacol 11(4): 271-6, June 1998; PTO 892) or Abdelaziz *et al* (Eur Respir J 10(4): 851-7; April 1997; PTO 892) or Barnes *et al* (Eur Respir J 7(3): 579-91, March 1994; PTO 892) or Hoshino *et al* (Allergy 52(8): 814-20, Aug 1997; PTO 892).

The teachings of Nagase *et al*, the '978 patent and '478 patent have been discussed supra.

The claimed invention as recited in claim 27 differs from the references only that the agent is administered to a mammal in conjunction with another agent selected from the group consisting of β-agonists, leukotriene modifiers (inhibitors or receptor antagonists), antihistamines, sodium cromoglycate, nedocrimal and theophylline.

Drazen *et al* teach leukotriene receptor antagonist such as (cysteinyl leukotriene (cysLT) and zafirlukast and 5-lipoxygenase (5-LO) inhibitor such as zileuton are safe and effective asthma treatment that improve pulmonary function and reduce airway inflammation, including inflammatory cell counts and airway hyperresponsiveness (See abstract, in particular).

Abraham *et al* teach agents such as cromolyn sodium (disodium cromoglycate) and beta 2 mimetic reproterol hydrochloride in combination gives better protection against post-antigen-induced airway hyperresponsiveness (AHR) than either one alone (See abstract, in particular).

Abdelaziz *et al* teach agent such as nedocromil sodium can reduce airway hyperresponsiveness by inhibiting eosinophil chemotaxis and adherence induced by human bronchial cell derived mediators (See abstract, in particular).

Barnes *et al* teach agent such as theophylline for treatment of asthma and is widely use as a bronchodilator and has anti-inflammatory activities such as inhibiting cytokines synthesis and release, and airway hyperresponsiveness (See abstract, in particular).

Hoshino *et al* teach an agent such as Ketotifen, which is an antihistamine, is beneficial for inhibiting activated eosinophils and T cell infiltration of inflammatory cells into the airway associated with asthma.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the leukotriene receptor antagonist and 5-lipoxygenase (5-LO) inhibitor as taught by Drazen *et al* or the cromolyn sodium as taught by Abraham *et al* or the nedocromil sodium as taught by Abdelaziz *et al* or the theophylline as taught by Barnes *et al* or the anti-histamine as taught by Hoshino *et al* with the Calcitonin Gene-related peptide (CGRP) as taught by Nagase *et al*. It would have been also obvious to one of ordinary skill in the art at the time the invention was made to substitute the corticosteroid, or the phosphodiesterase as taught by the '978 or the '478 patent for the leukotriene receptor antagonist and 5-lipoxygenase (5-LO) inhibitor as taught by Drazen *et al* or the cromolyn sodium as taught by Abraham *et al* or the nedocromil as taught by Abdelaziz *et al* or the theophylline as taught by Barnes *et al* or the anti-histamine as taught by Hoshino *et al* for a method to inhibit airway hyperresponsiveness in a mammal comprising administering to said mammal an agent in conjunction with other agents such as β-agonists, leukotriene modifiers (inhibitors or receptor antagonists), anti-histamines, phosphodiesterase inhibitors, sodium cromoglycate, nedocrimal and theophylline. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Drazen *et al* teach any leukotriene receptor antagonist and any 5-lipoxygenase (5-LO) inhibitors are effective for asthma since it improves pulmonary function and reduces airway inflammation, including inflammatory cell counts and airway hyperresponsiveness (See abstract, in particular). Abraham *et al* teach cromolyn sodium (disodium cromoglycate) and beta 2 mimetic reproterol hydrochloride in combination gives better protection against post-antigen-induced airway hyperresponsiveness (AHR) than either one alone (See abstract, in particular). Abdelaziz *et al* teach nedocromil sodium can reduce airway hyperresponsiveness by inhibiting eosinophil chemotaxis and adherence induced by human bronchial cell derived mediators (See abstract, in particular). Barnes *et al* teach agent such as theophylline is useful as a bronchodilator and has

anti-inflammatory activities such as inhibiting cytokines synthesis and release, including airway hyperresponsiveness (See abstract, in particular). Hoshino *et al* teach an agent any antihistamine, is beneficial for inhibiting activated eosinophils and T cell infiltration of inflammatory cells into the airway associated with asthma. Nagase *et al* teach Calcitonin Gene-related peptide (CGRP) is useful for inhibiting airway hyperresponsiveness (AHR) in a mammal. The '978 patent teaches calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat can inhibit acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness, in human (See column 5, lines 12-13, column 7, lines 45-49, claims of '978 patent, in particular). The '478 patent teaches agent such as calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat can inhibit acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness, in human (See column 13, lines 1-6, column 2, lines 39-66 column 3, lines 1-8, in particular).

18. Claims 1 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagase *et al* (Am J Respir Crit Care Med 154: 1551-56, 1996; PTO 1449) or US Pat No. 5,858,978 (Jan 1999; PTO 1449) or US Pat No. 5,635,478 (June 1997; PTO 1449) each in view of Cadieux *et al* (American J of Respiratory and Critical Care Medicine 159(1): 235-243, Jan 1999; PTO 1449).

The teachings of Nagase *et al*, the '978 patent and '478 patent have been discussed supra.

The claimed invention as recited in claim 12 differs from the references only that the agent is administered at a dose of from about 0.1 μg/kg (0.1 μg x kilogram^{-1}) and about 20 μg per kg (0 1 μg x kilogram^{-1}) body weight of said animal.

The claimed invention as recited in claim 13 differs from the references only that the agent is administered at a dose of from about 0.1 μg/kg (0.1 μg x kilogram^{-1}) and about 10 μg per kg (0 1 μg x kilogram^{-1}) body weight of said animal.

The claimed invention as recited in claim 14 differs from the references only that the agent is administered at a dose of from about 0.1 μg/kg (0.1 μg x kilogram^{-1}) and about 20 μg per kg (0.1 μg x kilogram^{-1}) body weight of said animal.

Cadieux *et al* teach administering an agent such as CGRP at 0.38 to 114 μg/kg body weight which is about 20 μg/kg, causes a dose related inhibition of substance P induced bronchoconstriction and attenuate substance P induced bronchoconstriction in guinea pig presensitized to allergen such as ovalbumin (See Abstract, in particular). Cadieux *et al* teach

CGRP acts as a potent broncoprotector agent on both guinea pig and human airway but its ability to limit the extent of airway responsiveness is strongly impaired in inflammatory conditions (Abstract, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the concentration in mg/kg body weight of CGRP as taught by the Nagase *et al*, the '978 patent or the '478 patent for the concentration in microgram per kg body weight as taught by Cadieux *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Cadieux *et al* teach administering an agent such as CGRP at 0.38 to 114 μg/kg body weight which is about 20 or 10 μg/kg, causes a dose related inhibition of substance P induced bronchoconstriction and attenuate substance P induced bronchoconstriction in guinea pig presensitized to allergen such as ovalbumin (See Abstract, in particular). The term "about" is open ended. It expands the claimed range to include the range taught by Cadieux *et al*. Claim 13 is included in this rejection because it is within the purview of one skill in the art at the time the invention was made to dilute the concentration and to administer an effective dose of CGRP for a method to inhibit airway hyperresponsiveness in a mammal as taught by Nagase *et al*, the '978 patent, the '478 patent and Cadieux *et al*.

19. Claims 1 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagase *et al* (Am J Respir Crit Care Med 154: 1551-56, 1996; PTO 1449) or US Pat No. 5,858,978 (Jan 1999; PTO 1449) or US Pat No. 5,635,478 (June 1997; PTO 1449) each in view of WO 97/09046 publication (March 1997; PTO 1449).

The teachings of Nagase *et al*, the '978 patent and the '478 patent have been discussed supra.

The claimed invention as recited in claim 15 differs from the references only by the recitation that the agent is a product of rational drug design that binds to and activates a CGRP receptor.

The WO 97/09046 publication teaches various agents such as ligand, which is CGRP receptor activity modifying protein (RAMP), that binds to and activates a CGRP receptor for a method of inhibiting asthma in all mammals, where asthma is associated with airway

hyperresponsiveness, in human (See entire document, abstract, page 9, lines 10-11, claims of WO 97/09046 publication, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the Calcitonin Gene-related peptide (CGRP) as taught by Nagase *et al*, the '978 patent, and the '478 patent or the homolog of Calcitonin Gene-related peptide (CGRP) as taught by the '978 patent, and the '478 patent for a method to inhibit airway hyperresponsiveness in a mammal comprising to a mammal a product of rational drug design that binds and activates a CGRP receptor. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 97/09046 publication teaches any agent that binds to and activates a CGRP receptor is useful for a method of inhibiting asthma in all mammals, where asthma is associated with airway hyperresponsiveness, in human (See entire document, abstract, page 9, lines 10-11, claims of WO 97/09046 publication, in particular). Nagase *et al* teach agent such as Calcitonin Gene-related peptide (CGRP) is useful for inhibiting airway hyperresponsiveness (AHR) in a mammal. The '978 patent teaches calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat can inhibit acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness, in human (See column 5, lines 12-13, column 7, lines 45-49, claims of '978 patent, in particular). The '478 patent teaches agent such as calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat can inhibit acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness, in human (See column 13, lines 1-6, column 2, lines 39-66 column 3, lines 1-8, in particular).

20. Claims 1 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagase *et al* (Am J Respir Crit Care Med 154: 1551-56, 1996; PTO 1449) in view of the WO 97/09046 publication (March 1997; PTO 1449).

The teachings of Nagase *et al* have been discussed supra.

The claimed invention as recited in claim 28 differs from the reference only by the recitation that the agent is administered to a mammal in conjunction with a CGRP receptor activity modifying protein (RAMP).

The WO 97/09046 publication teaches various agents such as ligands as well as antagonist, which is CGRP receptor activity modifying protein (RAMP), that binds to and activates a CGRP receptor for a method of inhibiting asthma in all mammals, where asthma is associated with airway hyperresponsiveness, in human (See entire document, abstract, page 9, lines 10-11, claims of WO 97/09046 publication, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the Calcitonin Gene-related peptide (CGRP) as taught by Nagase *et al* with the CGRP receptor activity modifying protein (RAMP) as taught by the WO 97/09046 publication for a method to inhibit airway hyperresponsiveness in a mammal comprising administering to said mammal an agent in conjunction with other agents such as CGRP receptor activity modifying protein (RAMP). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 97/09046 publication teaches CGRP receptor activity modifying protein (RAMP) is useful for inhibiting asthma in all mammals, where asthma is associated with airway hyperresponsiveness, in human (See entire document, abstract, page 9, lines 10-11, claims of WO 97/09046 publication, in particular). Nagase *et al* teach agent such as Calcitonin Gene-related peptide (CGRP) is useful for inhibiting airway hyperresponsiveness (AHR) in a mammal.

21. Claims 1 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,858,978 (Jan 1999; PTO 1449) or US Pat No. 5,635,478 (June 1997; PTO 1449) each in view of the WO 97/09046 publication (March 1997; PTO 1449).

The teachings of the '978 patent and the '478 patent have been discussed supra.

The claimed invention as recited in claim 28 differs from the references only by the recitation that the agent is administered to a mammal in conjunction with a CGRP receptor activity modifying protein (RAMP).

The WO 97/09046 publication teaches various agents such as ligands as well as antagonist, which is CGRP receptor activity modifying protein (RAMP), that binds to and activates a CGRP receptor for a method of inhibiting asthma in all mammals, where asthma is associated with airway hyperresponsiveness, in human (See entire document, abstract, page 9, lines 10-11, claims of WO 97/09046 publication, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the corticosteroid, or the phosphodiesterase as taught by the '978 and the '478 patent for the CGRP receptor activity modifying protein (RAMP) for a method to inhibit airway hyperresponsiveness in a mammal comprising administering to said mammal an agent in conjunction with other agents such as CGRP receptor activity modifying protein (RAMP). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 97/09046 publication teaches CGRP receptor activity modifying protein (RAMP) is useful for inhibiting asthma in all mammals, where asthma is associated with airway hyperresponsiveness, in human (See entire document, abstract, page 9, lines 10-11, claims of WO 97/09046 publication, in particular). The '978 patent teaches calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat can inhibit acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness, in human (See column 5, lines 12-13, column 7, lines 45-49, claims of '978 patent, in particular). The '478 patent teaches agent such as calcitonin gene-related peptide (CGRP) and homologue of CGRP such as CGRP from eel, salmon and rat can inhibit acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness, in human (See column 13, lines 1-6, column 2, lines 39-66 column 3, lines 1-8, in particular).

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

24. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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